

LETTER TO THE EDITOR



Statins and glycaemic control in type 2 diabetes: Are bile acids relevant?

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We read with interest the article by Ahmadizar et al¹ that suggests the use of statins may increase the risk of insulin resistance and type 2 diabetes (T2D). This population-based study has shown that ever use of statins is associated with a 38% higher risk of developing T2D (HR = 1.38; 95% CI, 1.09–1.74).¹ We congratulate the authors on their novel findings that addresses a clinically important question, prompted by evidence linking the use of higher potency statins² and lower low-density lipoprotein (LDL) targets³ to an increased risk of T2D. While the magnitude of this effect is likely to be modest—an estimated one additional case of diabetes per 255 patients treated over 4 years—particularly when compared with the benefits of preventing 5.4 vascular events in the same time period,⁴ it is still potentially important given the prevalent use of this drug class and incomplete understanding of the underlying mechanisms.

Hyperlipidaemia occurs in up to 50% of individuals with T2D and is associated with greater cardiovascular risk than in people with normal glucose tolerance.⁵ Accordingly, statins are recommended by the American Diabetes Association in all patients with T2D over the age of 40. It has been observed that when statins are used in combination with metformin (the most widely used glucose-lowering medication), they are associated with impaired glycaemic control, particularly at high doses.⁶

The mechanisms by which statins may disrupt glucose homeostasis remain incompletely understood. It has been suggested that statins may impair insulin secretion by inhibiting glucose-induced calcium signalling in pancreatic beta-cells, reducing the formation of by-products of cholesterol synthesis, such as coenzyme Q10 and dolichol, while also decreasing insulin-dependent glucose uptake via reduced GLUT4 recruitment.⁷ Statins may also reduce adiponectin levels and impair adipocyte maturation, to increase insulin resistance, although improvement of dyslipidaemia is intuitively beneficial.

One mechanism which has not, to our knowledge, been adequately explored is the impact of statins on bile acids, which are emerging as important metabolic regulators. Because statins block the production of cholesterol, the precursor of bile acids, their use has the potential to deplete the bile acid pool, particularly when enterohepatic circulation of bile acids is disturbed. In patients with interrupted enterohepatic circulation, who had undergone cholecystectomy, a single dose of simvastatin (80 mg) was shown to reduce biliary bile acid concentrations by >40%.⁸ By contrast,

administration of a lower dose of simvastatin (20 mg daily) over 3 months did not alter biliary bile acid output in patients with primary non-familial hypercholesterolaemia.⁹ Moreover, in mice, some statins appeared to increase faecal bile acids.¹⁰ However, the effect of statins on intestinal bile acids has not been evaluated in patients with T2D, in whom bile acid profiles often differ from those in health substantially.¹¹ Further studies in this group are therefore warranted.

When infused into various regions of the intestine, bile acids reduce glycaemic excursions following small intestinal glucose infusions and increase plasma levels of glucagon-like peptide-1 (GLP-1), an incretin hormone which potentiates insulin secretion, suppresses glucagon secretion, and slows gastric emptying.¹² The changes in bile acid circulation following bariatric surgery have been linked to improvement in glycaemic control.¹² In this regard, a reduction of luminal bile acids could contribute to impaired glucose tolerance, perhaps particularly after higher potency statins. Notably, individual bile acids may bind preferentially to different receptors, mediating distinct biological functions¹² and that bile acid sequestrants (which increase gastrointestinal exposure to less soluble bile acids) have been shown to improve glucose control in T2D.¹³ These observations have increased the complexity of the role of bile acids in glucose metabolism.

Metformin is the first-line choice of pharmacotherapy for T2D, with ~30% of patients failing to maintain adequate control.¹⁴ Despite being in clinical use for over 60 years, neither the mechanisms of its action, nor the factors accounting for its treatment failure, have been clearly elucidated. Recent evidence indicates that metformin lowers blood glucose primarily at the level of the gastrointestinal tract, at least in part, through stimulation of GLP-1 secretion. Clinical data suggest an indirect action, which may be related to inhibition of intestinal bile acid resorption induced by metformin.¹² Given statins and metformin are frequently used together in the management of type 2 diabetes, it is important to understand whether statins may compromise the glucose lowering effect of metformin by modulating the bile acid system.

Based on the findings of Ahmadizar et al, a potential for statins to disrupt glucose homeostasis should now be considered along with their cardiovascular benefits. Clarification of the mechanisms by which statins may impact on glycaemia in health and T2D, and the potential interactions of statins with glucose-lowering therapy, particularly metformin, may uncover novel targets for improved prevention and management of T2D.

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CONTRIBUTORS

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